Bayesian Hierarchical Modelling Approaches to Indirect Treatment Comparisons between Single-arm Basket Trials: *An Application to NTRK-fusion Solid Tumours*

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Disclosures

- AS was an employee at Cytel at the time of his contributions to this work. He is currently employed by AstraZeneca.

- Opinions expressed are our own and do not necessarily reflect the views of Inka Health, AstraZeneca, Cytel, or the Centre for Reviews and Dissemination at the University of York

Background

- Evaluating new drugs targeting rare cancer mutations/biomarkers can be extremely challenging due to difficulties recruiting enough patients
- Increased use of basket trial designs in recent years which recruit mutation/biomarker-positive patients with many different tumour types / histologies[1, 2]
- These basket trials are typically phase I/II, lack a concurrent control arm, focus on response endpoints, and have limited sample sizes both overall and within each tumour histology
- The need for estimates of comparative effectiveness vs. standard-of-care to evaluate the cost-effectiveness of these new treatments for health technology assessment (HTA) has been highlighted–for both specific histologies and for tumour-agnostic consideration[3, 4, 5, 6]

Objective

- Our goal is to demonstrate an indirect treatment comparison (ITC) method for basket trials which:
  - Compensates for potential confounding due to differences in histology composition between trials
  - Allows for partial pooling of information across histologies to improve precision/power where sample sizes are severely limited
  - Is implementable using aggregate data that is likely to be available from publications
- Our approach builds on some of our previous work, and established methods for applying BHMs in basket trial settings[7, 8, 9, 10, 11]
- We apply our approach to an ITC of two treatments–larotrectinib and entrectinib–studied in basket trial settings for NTRK-fusion positive solid tumours

Modelling Assumptions

- Our model relies on several key assumptions:
  - (i) Histologies are exchangeable (variability in prognosis across histologies can be modelled as random effects),
  - (ii) The distribution of prognostic factors within each histology is similar between basket trials,
  - (iii) There is overlap in included histologies between the two trials, and
  - (iv) (Optionally) relative treatment effects are constant across histologies.

- We consider an implementation that relaxes assumption (iv) by adding an additional random effect on the relative treatment effects

- We model the number of responders, r_{jk}, out of n_{jk} patients, for each basket trial $j \in \{0, 1\}$ and histology $k \in \{1, ..., K\}$ as follows:

$$\begin{aligned} r_{jk} &\sim \text{Binomial}(n_{jk}, p_{jk}) \\ \text{logit}(p_{jk}) &= \mu + d \cdot 1\{j = 1\} + \beta_k \\ \beta_k &\sim \text{N}(0, \sigma^2) \end{aligned}$$

- where μ is an intercept term, d is the relative treatment effect, β_k is the random effect for the tumour histology k, and σ^2 is the histology random-effect variance.
- We also consider a model variant which relaxes condition (iv) and instead assumes that relative treatment effects are also exchangeable across histologies, replacing d with

$$\delta_k \sim \text{N}(d, \tau^2)$$

- We opt to use weakly informative priors as follows:

$$\mu \sim \mathrm{N}\left(\mathrm{logit}(0.1), \left[\frac{1}{1.96}\left(\mathrm{logit}(0.9) - \mathrm{logit}(0.1)\right)\right]^2\right)$$

$$d \sim \mathrm{N}\left(0, \left[\frac{1}{2 \cdot 1.96}\left(\ln(10) - \ln(0.1)\right)\right]^2\right)$$

$$\sigma, \tau \sim \text{Half-Cauchy}(0, 1)$$

- We estimate our posteriors via Markov chain Monte Carlo (MCMC) implemented in Stan[12]. We use 100,000 iterations with a burn-in of 10,000 for each of 4 chains. MCMC convergence was assessed through trace plots.

Data (1 / 2)

- We use published aggregate data for entrectinib from the pooled phase-I ALKA-372-001 and STARTRK-1, and phase-II STARTRK-2 studies in adults with NTRK fusion-positive solid tumours[14].
- For larotrectinib we use published aggregate data for the pooled phase-I LOXO-TRK-14001 study in adults, phase-I/II SCOUT study in pediatric patients, and phase-II NAVIGATE study in pediatric and adult patients with NTRK-fusion-positive solid tumours[13].
- Using supplementary information from Hong et al.[13], we attempt to remove all pediatric larotrectinib patients (a total of 51 patients of whom 47 were responders)

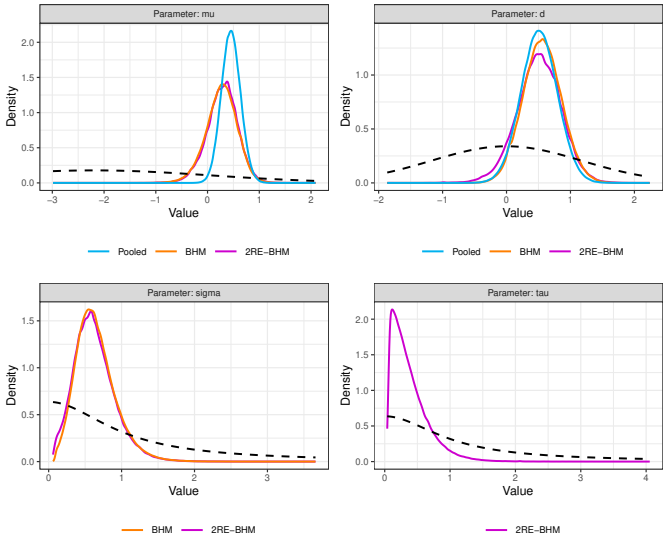
Data (2 / 2) – Responders and Observed Overall Response Rate (%)

Tumour Type	Larotrectinib	Entrectinib
Sarcoma	17 / 23 (74%)	15 / 26 (58%)
Thyroid	17 / 22 (77%)	7 / 13 (54%)
Salivary	18 / 20 (90%)	20 / 24 (83%)
Lung	9 / 12 (75%)	14 / 22 (64%)
Colorectal	4 / 8 (50%)	2 / 10 (20%)
Melanoma	3 / 6 (50%)	0 / 0 (–)
Breast	3 / 4 (75%)	5 / 7 (71%)
Pancreatic	1 / 2 (50%)	3 / 4 (75%)
Cholangiocarcinoma	1 / 2 (50%)	1 / 1 (100%)
Unknown Primary	1 / 1 (100%)	1 / 3 (33%)
Appendix	0 / 1 (0%)	0 / 0 (–)
Hepatocellular	0 / 1 (0%)	0 / 0 (–)
Neuroendocrine Tumours	0 / 0 (–)	2 / 5 (40%)
Gynecologic	0 / 0 (–)	1 / 2 (50%)
Head and Neck	0 / 0 (–)	2 / 2 (100%)
Adenocarcinoma of Upper GI Tract	0 / 0 (–)	1 / 1 (100%)
Neuroblastoma	0 / 0 (–)	0 / 1 (0%)
Pooled	74 / 102 (73%)	74 / 121 (61%)

- Note that there are 102 larotrectinib patients split across 12 histologies
- There are 121 entrectinib patients split across 14 histologies
- Many histologies contain only a few patients and only 9 / 17 histologies are present for both treatments

Key Parameter Posteriors under Each Model vs. Priors (Dashed Line)

- We compare posteriors vs. priors for a pooled approach, our basic BHM, and our 2-random effect BHM (“2RE-BHM”)
- Pooled treatment effect estimates (*d*)–the log odds ratio–are similar under all 3 models
- Evidence of modest heterogeneity in response across histologies but relatively minimal heterogeneity in relative treatment effect estimates



Pooled Treatment Effect Estimates

- Point estimates of the odds ratio (OR) of response are similar across all 3 modelling approaches
- 95% credible intervals (CrI) widen under the BHM and further widen under the 2RE-BHM, reflecting more uncertainty/restrained borrowing based on observed cross-histology heterogeneity
- Posterior probability of superiority for larotrectinib is high under all 3 models, however 95% CrIs include an OR of 1

Model	Median OR [95% CrI]	Prob. Superiority
Pooled	1.665 [0.963, 2.908]	0.966
BHM	1.743 [0.981, 3.168]	0.971
2RE-BHM	1.669 [0.819, 3.195]	0.928

Histology-Specific Treatment Effect Estimates

Histology	Median OR [95% CrI]	Prob. Superiority
Adenocarcinoma of Upper GI Tract	1.695 [0.463, 5.116]	0.849
Appendix	1.567 [0.353, 4.014]	0.800
Breast	1.716 [0.598, 4.736]	0.873
Cholangiocarcinoma	1.623 [0.458, 4.243]	0.830
Colorectal	1.657 [0.593, 4.056]	0.862
Gynecologic	1.692 [0.470, 5.155]	0.850
Head and Neck	1.693 [0.472, 5.150]	0.850
Hepatocellular	1.569 [0.348, 4.001]	0.799
Lung	1.743 [0.729, 4.227]	0.906
Melanoma	1.565 [0.465, 3.776]	0.814
Neuroblastoma	1.696 [0.472, 5.142]	0.850
Neuroendocrine Tumours	1.693 [0.463, 5.091]	0.850
Pancreatic	1.619 [0.454, 4.199]	0.829
Salivary	1.913 [0.845, 5.362]	0.942
Sarcoma	1.799 [0.838, 4.005]	0.937
Thyroid	1.888 [0.866, 4.649]	0.946
Unknown Primary	1.774 [0.596, 5.829]	0.881

- Posterior probability of superiority for larotrectinib is greater than 80% for all included tumour types, however, 95% CrIs still include OR of 1

Limitations

- This method relies on several strong assumptions, key among them that:
  - the random effects parameterization is considered to be an acceptable approximation for capturing cross-histology heterogeneity
  - there are no major remaining imbalances in baseline characteristics beyond histology that are likely to confound the treatment effect estimates
- Due to the severe data limitations encountered in basket trial settings, we argue that choice of ITC method should be viewed through the lens of determining an appropriate trade-off between precision and risk of bias

Discussion

- We demonstrate how a BHM ITC approach can be applied in practice to two drugs for NTRK-fusion positive solid tumours evaluated in single-arm basket trial settings
- We argue that this BHM ITC approach is better-suited to basket trial settings than many established population-adjusted indirect comparison methods such as those outlined by the NICE Decision Support Unit[15] (see also Mackay & Springford[16] for a discussion of the advantages of Bayesian approaches for HEOR/HTA decision-making for rare diseases)
- This approach can also be generalized to a comparison vs. an external control arm constructed using real-world data
- Manuscript preprint will be available very shortly–stay tuned!

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Thank You!

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